neurotransmitters, such as serotonin, can be attached to histones and facilitate gene expression in neurons[9].

In parallel, experimental approaches have become more sophisticated and informative. Several laboratory innovations are of particular interest for psychiatric epigenomics. First, single-cell approaches are redefining the meaning of epigenetic stochasticity and directly address the issues of cell type differences in the brain. Second, easily available somatic cells, such as fibroblasts, can be reprogrammed into neurons, partially addressing the need for brain tissue. Third, CRISPR-Cas9 technology can be used not only for editing genomes, but also epigenomes, which is of considerable interest for modeling disease components in tissue culture and animals. Fourth, progress in computational strategies has enabled the integration of epigenomic data with genomics, transcriptomics, and metabolomics. The comprehensive trans-omic approaches enable the identification of hub elements and cellular pathways centrally involved in disease. Given the rapid developments in molecular biology and brain imaging technologies, an ideal experiment – a prospective epigenomic study in the living brain of psychosis-predisposed individuals – may not be science fiction in the near future.

Despite the challenges thus far, epigenetics and epigenomics remain an important part of the psychiatric research agenda. There are still no better ways to explain the numerous dynamic features of complex diseases, which by definition do not conform with the stability of DNA sequence. Uncovering the mechanisms of discordance in monozygotic twins or the delayed age of psychosis onset would be of major importance for precision psychiatry. The success and progress of psychiatric epigenetics relies on the ever improving experimental and computational tools and, more importantly, on the diligence and creativity of scientists working on this very interesting, but also challenging, part of human biology.

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What is treatment resistance in psychiatry? A "difficult to treat" concept

Since the year 2000, there has been an exponential increase in papers on treatment resistant psychiatric disorders. It is unclear to what degree this is guided by unmet clinical need, by regulatory bodies looking for more homogeneous patient groups, or by budget limitations imposed by health care payers on first line treatments.

A more fundamental question is whether a categorical definition of treatment resistance makes sense[1,2]. Do we have evidence to delineate such an entity and, if so, what is the possible clinical practice benefit? When it results in putting a threshold before more effective treatment options can be implemented, why should those options not be chosen as an earlier treatment step? Anyhow, the concept underscores that currently available treatment options are suboptimal.

The evidence for a distinct psychopathological or neurobiological nature of treatment resistant psychiatric disorders, and hence for a categorical definition of treatment resistance, is limited and, outside of a clinical trial context, not very useful[3]. In depression, in anxiety disorders and in schizophrenia, the standard categorical definition is "an inadequate response to at least two adequate (appropriate dose and lasting for at least six weeks) treatment episodes with different drugs". In eating disorders, where psychopharmacology is not the main treatment option, treatment resistance has been poorly defined and shown to be mainly related to the severity of associated psychopathological features. In personality disorders, treatment resistance is often mentioned, but in the sense of resistance to entering or to pursuing psychotherapy.

What is supposed to be an inadequate response differs from disorder to disorder and is sometimes defined differently in a first step treatment versus a treatment resistant patient. A response can be considered inadequate on the basis of an absolute threshold of symptom severity or a percentage change from baseline in symptom severity[4]. In major depression and in generalized anxiety disorder, response is usually defined as a 50% decrease in symptom severity (but it has also been defined as a 25% decrease in patient selection for trials focusing on treatment resistant depression). In obsessive-compulsive disorder, it is usually defined as a 35% decrease in symptom severity, and in schizophrenia as a 30% decrease (or a 20% decrease in treatment resistant schizophrenia).

"Response" defined as a percentage improvement in the global score of a rating scale can obscure clinical reality: a response can be seen in a depressed patient despite high residual cogni-

tive symptoms or severe residual anhedonia, or in a patient with an anxiety disorder despite increased avoidance behavior, or in a patient with schizophrenia despite high levels of negative or cognitive symptoms. Functioning or distress are often not taken into account when defining an (in)adequate response, while, in some patients with schizophrenia, learning to cope with a treatment resistant hallucination can significantly decrease distress and hence improve quality of life[5].

The reason why most definitions of treatment resistance require two previous unsuccessful treatment episodes is also unclear. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial documented that, with each treatment step, an incremental gain in the response rate is observed, but there is also an incremental dropout rate and a higher and faster rate of relapse[6].

Furthermore, in defining treatment resistant schizophrenia, only pharmacotherapy is considered, while, in defining treatment resistant anxiety disorders, both pharmacotherapy and psychotherapy are taken into account. It is remarkable that, in treatment resistant depression, psychotherapy or neuromodulation (except electroconvulsive therapy) are most often not considered.

The fact that outcome in trials with treatment resistant patients provide different results depending on whether the two treatment episodes with inadequate response were both retrospective or whether one was retrospective and the other one prospective further documents the difficulty in obtaining a homogeneous patient population.

The recommendation that each of the two treatment episodes should have lasted "at least six weeks" is understandable from both a trial design and a clinical point of view, since few non-responders within the first six weeks will respond later, but again is far away from daily practice: health insurance databases show that a third treatment step is on average started after 43 weeks, which is important to take into account, since duration of an illness episode predicts outcome[7].

It is understandable that classification attempts are now moving away from two categories (non-resistant or resistant) versus staging and "levels of resistance" approaches. These are based on number of treatments (with different treatments getting differential weights), episode duration and symptom severity.

More fundamentally, it has been suggested that the expression "treatment resistance" is "devoid of empathy"[8]. Indeed, the expression seems to blame the disorder or even the patient: for example, a lay press article mentioned that a new antidepressant "can cause rapid antidepressant effects in many people with 'stubborn' depression"[9].

Finally, the concept of "treatment resistance" stems from an acute illness model with remission or cure as the goal. Unfortunately, not all patients with psychiatric disorders can reach that symptom-free goal. That's why the use of the more collaborative expression "difficult to treat" psychiatric disorders could be preferred.

This expression may fit better with the recurrent or chronic nature of some psychiatric disorders. Achieving a meaningful life in spite of limitations can be(come) the ultimate treatment goal. This also resonates with the "recovery" movement, which identifies regaining personal control and establishing a personally meaningful life, with or without residual symptoms, as the objective to pursue.

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Factors facilitating or preventing compulsory admission in psychiatry

A large majority of mental health professionals have a positive attitude towards compulsory admission of people with mental disorders, when some conditions specified by the law are present[1]. However, most professionals are not aware that the circumstances under which compulsory admissions actually occur worldwide are very different, as reflected by the wide variation of the numbers of these admissions in the various countries[2], which cannot be explained by clinical variables.

The factors which impact on the threshold for compulsory admissions, either facilitating or preventing them, can be classified into three levels: a macro-level, including the wider societal perspective and the national legislation; a meso-level, including the organization of mental health care and in particular the implementation of intervention strategies aimed to reduce those admissions; and a micro-level, including the socio-demographic and clinical features of the affected persons as well as the attitudes of their caregivers.

At the macro-level, the assumption that people with severe mental disorders, in particular schizophrenia, are unpredictable and dangerous is still widespread in the general population in many countries. This is the background on which national mental health legislations often identify the risk of harm to others as the main criterion for compulsory hospitalization, in order to ensure protection of the general public. The threshold for perceived danger may vary substantially from context to context and from professional to professional, and this will ob-